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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/892,485	06/28/2001	Mitsuko Ishihara	210577US0SRD	3202

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EXAMINER	
FORMAN, BETTY J	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 08/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/892,485	ISHIHARA ET AL.	
	Examiner	Art Unit	
	BJ Forman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70-88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

T.P

FINAL ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 23 May 2005 has been entered.

Status of the Claims

2. This action is in response to papers filed 23 May 2005 in which the previously examined claims were canceled and claims 70-88 were added. The amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action dated 23 December 2004 under 35 U.S.C. 112, first paragraph are withdrawn in view of the amendments. The previous rejections under 35 U.S.C. 103(a) are maintained. Applicant's arguments have been thoroughly reviewed and are discussed below.

Claims 70-88 are under prosecution.

Comments

3. The new claims are drawn to method for detecting an endocrine disrupting substance, with in combination with an endocrine hormone produces an endocrine disruption. The new claims recite the same method steps as the previously examined claims and differ only in the arrangement of the steps within the claims. For example, Previously examined Claim 29 compares gene expression from cells exposed to an endocrine hormone and test substance to

cells exposed only to the test substance, cells exposed only to the endocrine hormone and cells exposed to neither endocrine hormone or test substance to determine altered expression patterns. In a similar context, new Claim 70 compares gene expression from cells exposed to an endocrine hormone and test substance to cells exposed only to the test substance and cells exposed only to the endocrine hormone to determine "unique" expression. Claim 73 further compares the gene expression to cell exposed to neither endocrine hormone or test substance. Pages 15-16 of the instant specification define gene expression patterns as encompassing a wide range of analysis including total expression to expression of a specific gene. Therefore, the "unique" expression newly claimed, given the definition in the specification, encompassed the same scope as the previously examined claims.

> The term "gene expression pattern" used herein refers to total or partial information with regard to gene expression such as the type of a gene expressed in a cell under an arbitrary condition, the expression amount of the gene, or whether a specific gene is expressed or not. The range of the gene expression pattern may be arbitrarily selected by a test performer depending upon various conditions.
>
> The term "a gene specific to a first gene expression pattern" used herein refers to a gene specifically expressed by the action of an endocrine disrupting substance, a gene whose expression is suppressed by the action of an endocrine disrupting substance, and a gene whose expression amount and/or transcription amount varies specifically by the action of an endocrine disrupting substance. The term "variation of the expression amount and/or transcription amount" includes all changes-increase and decrease.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 70, 73, 81-84, 86-88 are rejected under 35 U.S.C. 102(b) as being anticipated by Nilsson et al (U.S. Patent No. 5,578,445, issued 26 November 1996).

Regarding Claims 70 and 73, Nilsson et al disclose a method for detecting an endocrine disrupting substance, which in combination with an endocrine hormone disrupts endocrine, the method comprising culturing a cell sensitive to an endocrine hormone in the presence of the hormone (i.e. reference substance) and a test substance and detecting a gene expression pattern of said cell and comparing the expression pattern to the cell cultured in the absence of the test substance and the cell cultured in the presence of the test substance and the cell cultured in the absence of the hormone and test substance wherein unique (i.e. different) expression is indicative of endocrine disruption (Column 1, lines 39-Column 2, line 14) wherein the combination of endocrine hormone and the test substance disrupts endocrine. As illustrated in the table at the top of column 6, pS2 expression is lowest in the presence of both the endocrine hormone and test substance. Furthermore, they provide specific embodiments wherein the reference sequence is estradiol (defined as a female hormone in the instant specification, page 10, lines 20-22) and the test substance is tamoxifen (Column 5, line 26-Column 6, line 23 and Claim 1) wherein the cells are not obtained by genetic engineering i.e. MCF7 cell lines (Column 5, lines 25-28).

Regarding Claim 81, Nilsson et al disclose the method wherein the cell is a normal cell (Column 2, line 54-Column 3, line 3).

Regarding Claim 82, Nilsson et al disclose the method wherein the cell is a cancer cell (Column 5, line 26-45).

Regarding Claim 83, Nilsson et al disclose the method wherein the cell is a human cell (Column 2, lines 54-58).

Regarding Claim 84, Nilsson et al disclose the method wherein the cell is a nonhuman cell as taught by contrast to their preferred embodiment wherein the cell is human (Column 2, lines 54-58).

Regarding Claim 86, Nilsson et al disclose the method wherein the cell is MCF7 (Column 5, lines 26-28).

Regarding Claim 87, Nilsson et al disclose the method wherein the hormone is a female hormone i.e. estradiol (defined as a female hormone in the instant specification, page 10, lines 20-22) (Column 5, lines 45-54).

Regarding Claim 88, Nilsson et al disclose the method wherein the hormone is estradiol (Column 5, lines 45-54).

Response to Arguments

6. Applicant asserts that the newly claimed method for determining an endocrine disruption based on a combination of endocrine hormone and test substance is not taught by Nilsson et al because, in contrast to the instant invention, Nilsson et al are interested in drugs having antagonistic or agonistic effects. The argument has been considered but is not found persuasive because, as cited above, Nilsson et al clearly illustrates endocrine disruption pS2 expression in the presence of endocrine hormone (estradiol) and test substance (tamoxifen) (Column 6, lines 1-8). While Nilsson et al may be interested in agonists and/or antagonists, they clearly perform the claimed method steps resulting in the method as claimed.

Applicant asserts that the instant invention, unlike Nilsson et al, cause gene expression entirely different from gene expression induced only by the hormone. The argument has been considered but is not found persuasive because, as noted above, the method of Nilsson et al illustrates that combination of estradiol and tamoxifen causes pS2 gene to be expressed differently from that in the presence of estradiol alone.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 71-72, 74-76, 80 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al (U.S. Patent No. 5,578,445, issued 26 November 1996) in view of Falb (U.S. Patent No. 5,849,578, issued 15 December 1998).

Regarding Claim 71-72 and 74-75 Nilsson et al disclose a method for detecting an endocrine disrupting substance, which in combination with an endocrine hormone disrupts endocrine, the method comprising culturing a cell sensitive to an endocrine hormone in the presence of the hormone (i.e. reference substance) and a test substance and detecting a gene expression pattern of said cell and comparing the expression pattern to the cell cultured in the absence of the test substance and the cell cultured in the presence of the test substance and the cell cultured in the absence of the hormone and test substance wherein unique (i.e. different) expression is indicative of endocrine disruption (Column 1, lines 39-Column 2, line 14) wherein the combination of endocrine hormone and the test substance disrupts endocrine. As illustrated in the table at the top of column 6, pS2 expression is lowest in the presence of both the endocrine hormone and test substance. Furthermore, they provide specific embodiments wherein the reference sequence is estradiol (defined as a female hormone in the instant specification, page 10, lines 20-22) and the test substance is tamoxifen (Column 5, line 26-Column 6, line 23 and Claim 1) wherein the cells are not obtained by genetic engineering i.e. MCF7 cell lines (Column 5, lines 25-28).

Nilsson et al does not teach analysis of gene expression pattern by determining variation in gene expression based on an electrophoretic pattern of RNA or cDNA recovered from the cells. However, electrophoresis for expression analysis was well known and routinely practiced in the art at the time the claimed invention was made as taught by Falb.

Falb teaches a similar method for determining endocrine disrupting activity of a test substance comprising culturing normal cells in the presence and absence of the test substance

and comparing gene expression to determine disruption (Column 74, lines 7-67). Furthermore, they provide specific preferred methods for expression comparison (sections 6.1.2 and 8.1) the methods comprising recovering the RNAs, reverse transcribing the RNA, amplifying the transcription products and subjecting the amplified products to electrophoresis (Column 16, line 53-Column 18, line 65). Falb further teaches the RNA isolation, hybridization, subtraction, amplification and detection provides identification of genes differentially expressed is samples of interest (Column 16,lines 54-59). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the gene expression analysis of Nilsson et al with the RNA isolation, hybridization, subtraction, amplification and detection taught by Falb for the expected benefit of identifying sample-specific gene expression as desired in the art as taught by Falb (Column 16, lines 54-59).

Regarding Claim 76, Nilsson et al disclose a method for detecting an endocrine disrupting action of a test substance comprising culturing a cell sensitive to an endocrine hormone in the presence of the hormone (i.e. reference substance) and a test substance and detecting a gene expression pattern of said cell and comparing the expression pattern to the cell cultured in the absence of the test substance or the cell cultured in the absence of the hormone but the presence of the test substance or the cell cultured in the absence of the hormone and test substance wherein increased or decreased expression is indicative of endocrine disruption (Column 1, lines 39-Column 2, line 14) Furthermore, they provide specific embodiments wherein the reference sequence is estradiol (defined as a female hormone in the instant specification, page 10, lines 20-22) and the test substance is tamoxifen (Column 5, line 26-Column 6, line 23 and Claim 1) wherein the expression patterns are measured by determining the variation is the amount of gene expression i.e. protein expression regulated by gene expression (Column 3, lines 11-17).

Nilsson does not teach determining gene expression by recovering RNA from the cells and comparing for each cell treatment the RNA or cDNA from the RNA from the treated cells to determining endocrine disruption.

However, gene expression via RNA hybridization comparisons were well known in the art at the time the claimed invention was made as taught by Falb.

Falb teaches a similar method for determining endocrine disrupting activity of a test substance comprising culturing cells in the presence and absence of the test substance and comparing gene expression to determine disruption (Column 73, line 45-Column 74, line 35). Furthermore, they provide specific preferred methods for expression comparison (sections 6.1.2 and 8.1) the methods comprising recovering the RNAs, reverse transcribing the RNA, amplifying the transcription products and subjecting the amplified products to electrophoresis (Column 16, line 53-Column 18, line 65). Falb further teaches the RNA isolation, hybridization, subtraction, amplification and detection provides identification of genes differentially expressed is samples of interest (Column 16,lines 54-59). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the gene expression analysis of Nilsson et al with the RNA isolation, hybridization, subtraction, amplification and detection taught by Falb for the expected benefit of identifying sample-specific gene expression as desired in the art as taught by Falb (Column 16, lines 54-59).

Regarding Claim 80 and 85, Nilsson et al disclose a method for detecting an endocrine disrupting action of a test substance comprising culturing a cell sensitive to an endocrine hormone in the presence of the hormone (i.e. reference substance) and a test substance and detecting a gene expression pattern of said cell and comparing the expression pattern to the cell cultured in the absence of the test substance or the cell cultured in the absence of the hormone but the presence of the test substance or the cell cultured in the absence of the hormone and test substance wherein increased or decreased expression is indicative of endocrine disruption (Column 1, lines 39-Column 2, line 14). Furthermore, they provide

specific embodiments wherein the reference sequence is estradiol (defined as a female hormone in the instant specification, page 10, lines 20-22) and the test substance is tamoxifen (Column 5, line 26-Column 6, line 23 and Claim 1).

Nilsson et al teach method wherein endocrine disruption of a test substance is analyzed in various cell and tissues whereby effects of the test substance in the cells or tissues is analyzed (Column 2, lines 54-66) and useful as a tool for predicting effects of test substances as drug candidates (Column 1, lines 11-30). Nilsson et al further teach the preferred embodiment evaluates any steroid hormone, thyroid hormone or glucocorticoid hormones (Column 3, lines 4-8). These teachings clearly suggest the method is applicable for any cell or tissue sensitive to any endocrine hormone. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the specific embodiments taught by Nilsson by analyzing any cells (e.g. nerve cells or germ cells or murine) for any endocrine hormone (e.g. androgen, testosterone, adrenal cortex hormone, cortisol, aldosterone, amino acid derivative hormone, T3, T4 or parathyroid hormone) for the expected benefit of studying the effects of candidate drugs in cells of interest for modification of clinically important endocrine hormones as suggested by Nilsson et al (Column 1, lines 11-30).

Response to Arguments

9. Applicant relies on the arguments regarding Nilsson et al to traverse the above rejections. The arguments are noted but not found persuasive for the reasons stated above regarding Nilsson et al.

10. Claims 77-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al (U.S. Patent No. 5,578,445, issued 26 November 1996) in view of Falb (U.S. Patent No. 5,849,578, issued 15 December 1998) as applied to Claim 29 above and further in view of Horwitz et al (U.S. Patent No. 6,750,015, filed 21 March 2001)

Regarding Claims 77-79, Nilsson et al disclose a method for detecting an endocrine disrupting action of a test substance comprising culturing a cell sensitive to an endocrine hormone in the presence of the hormone (i.e. reference substance) and a test substance and detecting a gene expression pattern of said cell and comparing the expression pattern to the cell cultured in the absence of the test substance or the cell cultured in the absence of the hormone but the presence of the test substance or the cell cultured in the absence of the hormone and test substance wherein increased or decreased expression is indicative of endocrine disruption (Column 1, lines 39-Column 2, line 14) wherein gene expression patterns are measured by determining a variation in the amount of protein expressed between A, B, C or D (Column 3, lines 11-17 and Column 5, line 65-Column 6, line 8). Nilsson et al do not teach electrophoresis, SDS-PAGE, two-dimensional electrophoresis to measure protein expression however measuring protein expression was well known in the art at the time the claimed invention was made as taught by Horwitz et al who teach a similar method for analyzing endocrine hormone responsive gene expression wherein the gene expression is determined by measuring proteins using electrophoresis e.g. SDS-PAGE (Column 49, line 55-Column 50, line 14). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the protein expression measuring of Nilsson et al by utilizing well known protein measurements e.g. electrophoresis, SDS-PAGE or two-dimensional electrophoresis because one of ordinary skill would have had reasonable expectation of success using well know techniques.

Response to Arguments

11. Applicant relies on the arguments regarding Nilsson et al to traverse the above rejections. The arguments are noted but not found persuasive for the reasons stated above regarding Nilsson et al.

12. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (571) 272-0741. The examiner can normally be reached on 6:00 TO 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the

number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

BJ Forman, Ph.D.
Primary Examiner
Art Unit: 1634
August 11, 2005